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- (21) International Application Number: PCT/GB2004/004133 (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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- Published:**  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **POLYMORPHIC FORMS OF A KNOWN ANTIHYPERLIPEMIC AGENT**

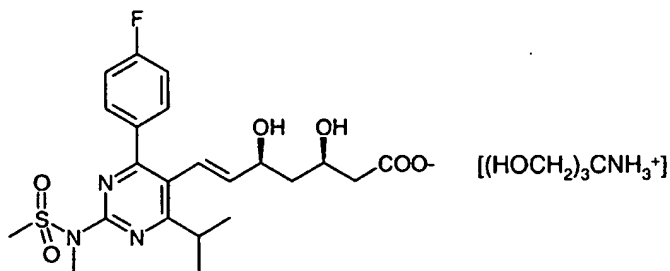
(57) Abstract: Two new polymorphic forms of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-en oic acid tris(hydroxymethyl)methylammonium salt (1), processes for making them and their use in the production of a pharmaceutical useful in the treatment of, *inter alia*, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis are described.



**WO 2005/028450 A1**

## POLYMORPHIC FORMS OF A KNOWN ANTIHYPERLIPEMIC AGENT

This invention concerns new polymorphic forms of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid tris(hydroxymethyl)methylammonium salt (1) (illustrated below), which is useful for the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.



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The sodium salt and calcium salt of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid (hereinafter referred to as compound (2)) were disclosed in European Patent 0521471. This patent also describes a process for the synthesis of the calcium salt, via the sodium salt.

Our International Patent Application WO 00/42024 discloses a crystalline form of the calcium salt of (2), and processes for making it.

Our International Patent Application WO 01/60804 discloses alternative crystalline salts of (2). One of these salts is the tris(hydroxymethyl)methylammonium salt (1). In this application, the process exemplified for formation of tris(hydroxymethyl)methylammonium salt is: acidification of a solution of the methylamine salt of (2) in acetonitrile and water, separation and drying of the organic layer followed by addition of tris(hydroxymethyl)aminomethane at ambient temperature, collection of the crystalline product at ambient temperature and then drying of the crystals at 30°C under vacuum. This process produces needle shaped crystals of a single polymorph of the salt (1) with an X-ray powder diffraction pattern with peaks at 2-theta = 7.9, 8.5, 10.2, 16.7, 18.4, 19.3, 19.8, 20.2, 21.5 and 24.9°.

We have discovered two further polymorphic crystalline forms of the tris(hydroxymethyl)methylammonium salt (1) herein called Forms 2 and 3. Such polymorphic forms may have different solubilities and/or stabilities and/or bioavailabilities

and/or different impurity profiles (minor impurities which arise for example because of the process of manufacture and/or isolation) and/or crystal forms which are easier to handle, micronise and/or form into tablets.

According to one aspect of the invention is provided a crystalline  
5 tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid having an X-ray powder diffraction pattern with peaks at 2-theta = 3.2, 6.3, 9.5 and 11.0. This crystalline form is hereinafter referred to as Form 2.

According to another aspect of the invention there is provided Form 2 having an X-ray  
10 powder diffraction pattern with peaks at 2-theta = 3.2, 6.3, 9.5, 11.0, 12.0, 12.4, 13.9 and 21.5.

According to another aspect of the invention is provided Form 2 having an X-ray powder diffraction pattern with peaks at 2-theta = 3.2, 6.3, 9.5, 11.0, 12.0, 12.4, 13.9, 15.8, 21.5, 22.7, 23.6 and 24.9.

15 According to another aspect of the invention is provided Form 2 having an X-ray powder diffraction pattern substantially as shown in Figure 1.

It will be appreciated that the 2-theta values listed in the aspects of the invention hereinbefore for Form 2, and hereinafter for Form 3, are chosen because they most clearly differentiate one Form from another, although they do not necessarily represent the most  
20 intense peaks.

The Form 2 polymorphic salt of this aspect of the invention may be produced by the following process: a sample of amorphous tris(hydroxymethyl)methylammonium salt (1) (which may be prepared by freeze drying an aqueous solution of the salt (1)) is slurried in a suitable organic solvent at a temperature below ambient temperature, the resultant mixture is  
25 filtered and the resulting product is dried as necessary.

Suitable organic solvents may be determined experimentally by the skilled person. Conveniently, the organic solvent is acetonitrile, ethyl acetate or MTBE (methylt-butylether).

Conveniently the mixture is slurried for an extended period, for example for 24 hours. Conveniently, the mixture is slurried at a temperature below ambient temperature which is for  
30 example, between about 0°C and 10°C, such as between about 0°C and 5°C, and preferably at about 0°C.

The product is conveniently dried by prolonged filtration under vacuum, the use of temperatures above ambient temperature preferably being avoided in order to avoid any risk of conversion of polymorphic form.

It will be appreciated that Form 2 may be produced by alternative methods, for example crystallisation from a solution in a suitable organic solvent at low temperature.

According to a further aspect of the invention there is provided a crystalline tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid having an X-ray powder diffraction pattern with peaks at 2-theta = 6.9 and 13.1. This crystalline form is hereinafter referred to as Form 3.

According to a further aspect of the invention there is provided Form 3 having an X-ray powder diffraction pattern with peaks at 2-theta = 6.9, 13.1, 14.9 and 20.6.

According to a further aspect of the invention there is provided Form 3 having an X-ray powder diffraction pattern with peaks at 2-theta = 6.9, 8.5, 9.0, 13.1, 14.9, 17.2, 18.2, 18.6, 19.0, 19.4, 20.6 and 25.4.

According to another aspect of the invention there is provided Form 3 having an X-ray powder diffraction pattern substantially as shown in Figure 2.

The Form 3 polymorphic salt of the above aspects of the invention may be produced by the following process: a sample of amorphous tris(hydroxymethyl)methylammonium salt (1) (which may be prepared by freeze drying an aqueous solution of the salt (1)) is slurried in isopropanol at a temperature below ambient temperature, the resultant mixture is filtered and the resulting product is dried.

Conveniently the mixture is slurried for an extended period, for example for 24 hours. Conveniently, the mixture is slurried at a temperature below ambient temperature which is, for example, between about 0°C and 10°C, such as between about 0°C and 5°C, and preferably at about 0°C.

The product is conveniently dried by prolonged filtration under vacuum, the use of temperatures above ambient temperature preferably being avoided in order to avoid any risk of conversion of polymorphic form.

Thermal Gravimetric Analysis of samples of Form 3 indicates that the polymorphic form is solvated, which arises from the method of manufacture and will be water and/or isopropanol.

Form 2 and Form 3 may also be characterised by any suitable method known in the art.

The X-ray powder diffraction spectra were determined by mounting a sample of the crystalline form on Siemens single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated x-ray source was passed through an automatic variable divergence slit set at V20 (20mm path length) and the reflected radiation directed through a 2mm antiscatter slit and a 0.2mm detector slit. The sample was exposed for 4 seconds per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 2 hours 6 minutes and 40 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a DECpc LPv 433sx personal computer running with Diffrac AT (Socabim) software.

It will be understood that the 2-theta values of an X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample to another, and so the values quoted are not to be construed as absolute. It will also be understood that the relative intensities of peaks may vary according to the orientation of the sample under test so that the intensities in the XRD traces included herein are illustrative and not intended to be used for absolute comparison.

Forms 2 and 3 obtained according to the present invention are substantially free from other crystal and non-crystal forms of tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid. The term "substantially free from other crystal and non-crystal forms" shall be understood to mean that the desired crystal form (Form 2 or Form 3) contains less than 50%, preferably less than 10%, more preferably less than 5% of any other forms of the tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid.

The utility of the compounds of the invention may be demonstrated by standard tests and clinical studies, including those described in EPA 521471.

According to a further feature of the invention is a method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises

administering to a warm-blooded mammal an effective amount of Form 2 or Form 3. The invention also relates to the use of Form 2 or Form 3 in the manufacture of a medicament for use in a disease condition.

The compound of the invention may be administered to a warm-blooded animal, particularly a human, in need thereof for treatment of a disease in which HMG CoA reductase is implicated, in the form of a conventional pharmaceutical composition. Therefore in another aspect of the invention, there is provided a pharmaceutical composition comprising Form 2 or Form 3 in admixture with a pharmaceutically acceptable carrier.

Such compositions may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes Form 2 or Form 3 may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solution or suspensions or sterile emulsions. A preferred route of administration is oral. Form 2 or Form 3 will be administered to humans at a daily dose in, for example, the ranges set out in EPA 521471. The daily doses may be given in divided doses as necessary, the precise amount of the Form received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

According to a further feature of the invention, there is provided a process for the manufacture of a pharmaceutical composition containing Form 2 or Form 3 as active ingredient, which comprises admixing Form 2 or Form 3 together with a pharmaceutically acceptable carrier.

It will be appreciated that Form 2 and Form 3 may be converted to alternative salts of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid, such as the sodium or calcium salt, and the alternative salt may then be used for treatment of a disease in which HMG CoA reductase is implicated, for example as a pharmaceutical composition, as hereinbefore described for Form 2 and Form 3.

Therefore in a further aspect of the invention, there is provided the use of Form 2 or Form 3 as an intermediate in the manufacture of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

[methyl(methylsulfonyl)amino]pyrimidin-5-yl)-(3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt.

Isolation of a crystalline salt, such as Form 2 or Form 3, allows purification by re-crystallisation if necessary. This may be advantageous where, for example, an alternative, non-crystalline salt form is required. Thus a crystalline salt form can be used as a processing aid in the manufacture of non-crystalline salt forms, or crystalline salt forms whose properties are such that purification by re-crystallisation is not straightforward. In particular, it is known that the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl)-(3R,5S)-3,5-dihydroxyhept-6-enoic acid is generally amorphous unless crystallised under specific conditions.

In a further aspect of the invention, there is provided the use of Form 2 or Form 3 as a processing aid in the manufacture of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl)-(3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt.

The invention is further illustrated, but not limited by the following examples.

#### **Example 1**

Amorphous tris(hydroxymethyl)methylammonium salt (1) (1 g), prepared by freeze-drying an aqueous solution of the salt (which may be prepared according to the method described in WO 01/60804), was added to acetonitrile (10 ml) at 0°C and stirred at 0°C for 24 h. The slurry was filtered under vacuum to dryness to yield tris(hydroxymethyl)methylammonium salt (1) Form 2.

<sup>1</sup>H NMR (d6-DMSO) δ: 1.22 (dd, 6H), 1.36 (m, 1H), 1.52 (m, 1H), 2.07 (m, 1H), 2.19 (m, 1H), 3.37 (s, 6H), 3.45 (s, 3H), 3.55 (s, 3H), 3.76 (m, 1H), 4.21 (q, 1H), 5.54 (dd, 1H), 6.51 (dd, 1H), 7.28 (t, 2H), 7.72 (m, 2H)

#### **Example 2**

Amorphous tris(hydroxymethyl)methylammonium salt (1) (1 g), prepared by freeze-drying an aqueous solution of the salt, was added to ethyl acetate (10 ml) at 0°C and stirred at 0°C for 24 h. The slurry was filtered under vacuum to dryness to yield tris(hydroxymethyl)methylammonium salt (1) Form 2.

**Example 3**

Amorphous tris(hydroxymethyl)methylammonium salt (1) (1 g), prepared by freeze-drying an aqueous solution of the salt, was added to MTBE (10 ml) at 0°C and stirred at 0°C for 24 h.

The slurry was filtered under vacuum to dryness to yield

5 tris(hydroxymethyl)methylammonium salt (1) Form 2.

**Example 4**

Amorphous tris(hydroxymethyl)methylammonium salt (1) (1 g), prepared by freeze-drying an aqueous solution of the salt, was added to isopropyl alcohol (10 ml) at 0°C and stirred at 0°C

10 for 24 h. The slurry was filtered under vacuum to dryness to yield  
tris(hydroxymethyl)methylammonium salt (1) Form 3.

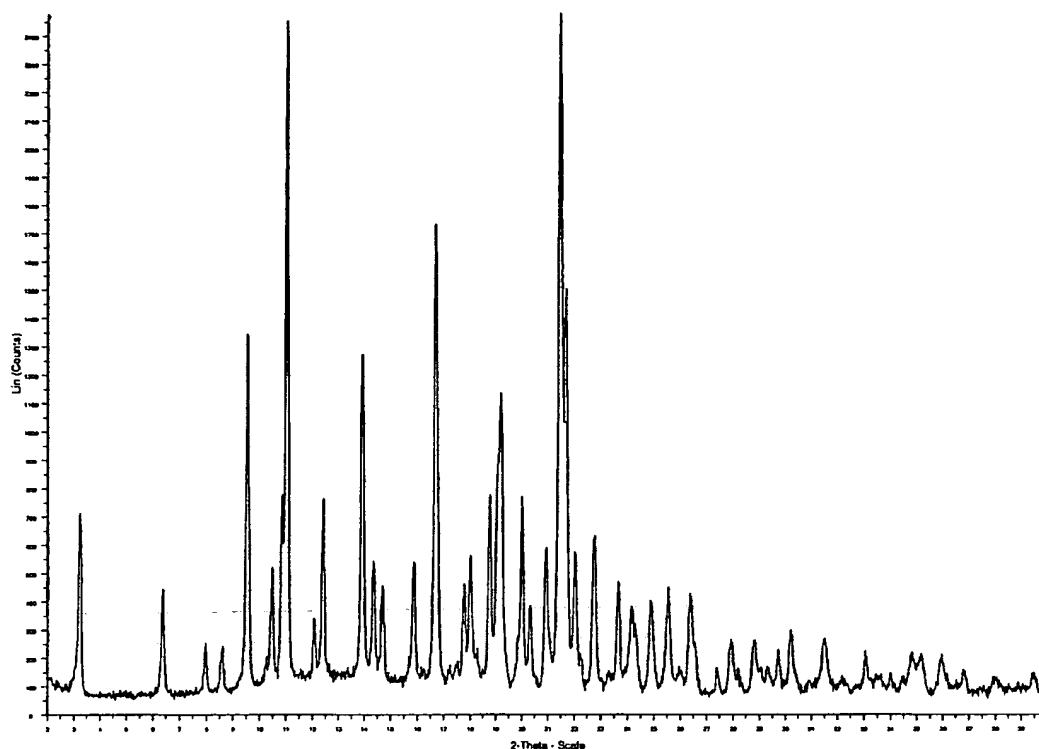
<sup>1</sup>H NMR (d6-DMSO) δ: 1.04 (d, from isopropyl alcohol), 1.22 (dd, 6H), 1.36 (m, 1H), 1.52 (m, 1H), 2.07 (m, 1H), 2.19 (m, 1H), 3.37 (s, 6H), 3.45 (s, 3H), 3.55 (s, 3H), 3.76 (m, 1H), 3.78 (m, from isopropyl alcohol), 4.21 (q, 1H), 5.54 (dd, 1H), 6.51 (dd, 1H), 7.28 (t, 2H), 7.72  
15 (m, 2H).

Identity of the samples were confirmed by <sup>1</sup>H NMR. <sup>1</sup>H NMR were analysed using a Bruker DPX400 operating at a field strength of 400MHz, using d6-dimethylsulfoxide as a solvent.. Chemical shifts were measured in parts per million relative to tetramethylsilane.

20 Peak multiplicities are expressed as follows: s = singlet, d = doublet, q = quartet, t = triplet, m = multiplet.

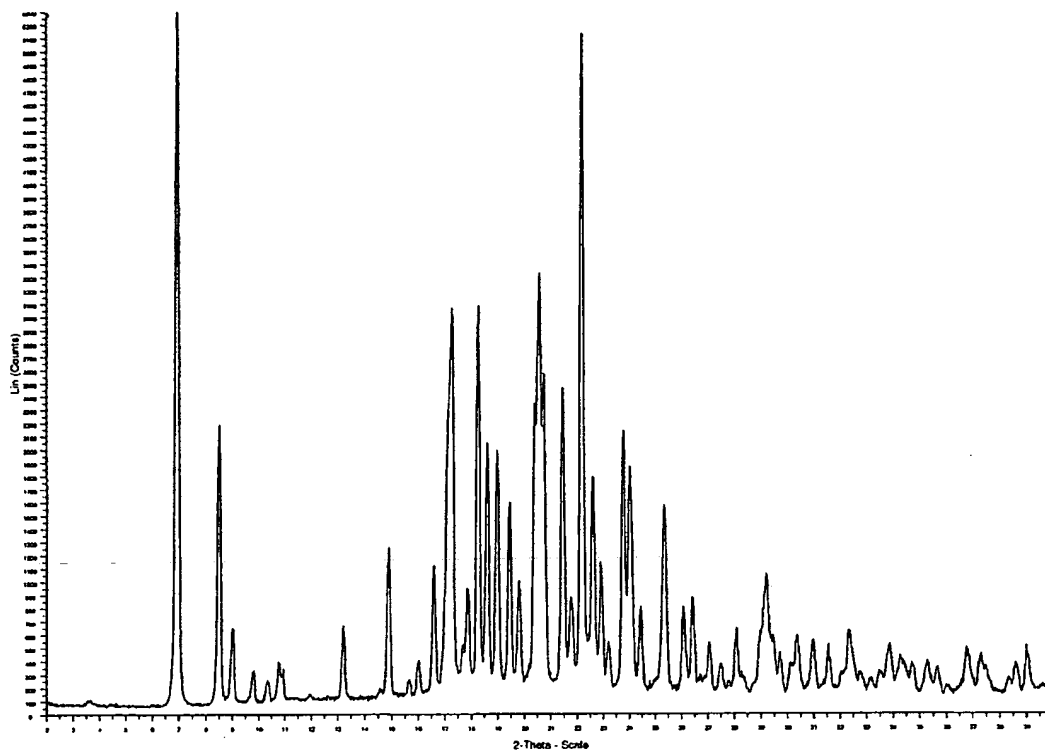


**Figure 1. Tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid Form 2**



2-theta	d-spacing	Relative Intensity
3.2	27.8	29
6.3	14.0	18
9.5	9.3	54
11.0	8.0	99
12.0	7.4	14
12.4	7.2	31
13.9	6.4	51
15.8	5.6	22
21.5	4.1	100
22.7	3.9	25
23.6	3.8	19
24.9	3.6	16

**Figure 2 – Tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid Form 3**

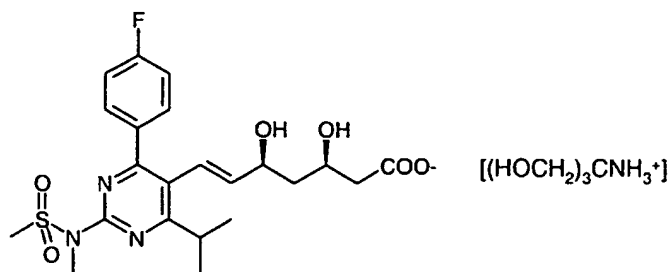


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2-theta	d-spacing	Relative Intensity
6.9	12.8	100
8.5	10.5	41
9.0	9.9	12
13.1	6.7	13
14.9	6.0	24
17.2	5.1	58
18.2	4.9	58
18.6	4.8	39
19.0	4.7	38
19.4	4.6	30
20.6	4.3	63
25.4	3.5	30

**Claims**

1. A crystalline form of the compound tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid of the formula (I) having an X-ray powder diffraction pattern with specific peaks at 2-theta = 3.2, 6.3, 9.5 and 11.0.



(I)

2. A crystalline form as claimed in Claim 1 having an X-ray powder diffraction pattern with specific peaks at 2-theta = 3.2, 6.3, 9.5, 11.0, 12.0, 12.4, 13.9 and 21.5.
3. A crystalline form as claimed in Claim 1 having an X-ray powder diffraction pattern with specific peaks at 2-theta = 3.2, 6.3, 9.5, 11.0, 12.0, 12.4, 13.9, 15.8, 21.5, 22.7, 23.6 and 24.9.
4. A crystalline form of the compound tris(hydroxymethyl)methylammonium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid having an X-ray powder diffraction pattern with specific peaks at 2-theta = 6.9 and 13.1.
5. A crystalline form as claimed in Claim 4 having an X-ray powder diffraction pattern with specific peaks at 2-theta = 6.9, 13.1, 14.9 and 20.6.
6. A crystalline form as claimed in Claim 4 having an X-ray powder diffraction pattern with specific peaks at 2-theta = 6.9, 8.5, 9.0, 13.1, 14.9, 17.2, 18.2, 18.6, 19.0, 19.4, 20.6 and 25.4.

5. A pharmaceutical composition comprising a crystalline form as claimed in any one of the preceding claims, together with a pharmaceutically acceptable carrier.

6. A process for the manufacture of a pharmaceutical composition as claimed in claim 5  
5 which comprises admixing a crystalline form as claimed in Claim 1 or Claim 4 together with a pharmaceutically acceptable carrier.

7. The use of a crystalline form as claimed in Claim 1 or Claim 4 in the manufacture of a medicament.

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8. A method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of a crystalline form as claimed in Claim 1 or Claim 4.

15 9. A process for the manufacture of a crystalline form as claimed in Claim 1 or Claim 4 which comprises forming crystals by:

a) slurring a sample of amorphous tris(hydroxymethyl)methylammonium salt (1) in an organic solvent at a temperature below ambient temperature;

b) filtration of the resultant mixture; and

20 c) drying of the resultant product as necessary.

10. A process as claimed in Claim 9 for the manufacture of Form 2 wherein the organic solvent is acetonitrile, ethyl acetate or MTBE (methylt-butylether).

25 11. A process for the manufacture of a crystalline form as claimed in Claim 9 for the manufacture of Form 3 wherein the organic solvent is isopropanol.

12. A process as claimed in any one of Claims 9 to 11 wherein the temperature is about 0°C.

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# INTERNATIONAL SEARCH REPORT

PCT/GB2004/004133

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/42 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/60804 A (TAYLOR NIGEL PHILIP ; ASTRAZENECA UK LTD (GB); SHIONOGI & CO (JP); OKA) 23 August 2001 (2001-08-23) page 3, line 6 - page 5, line 24; example 2	1-12
A	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) page 2, line 9 - page 2, line 29	1-12
P, X	WO 2004/014872 A (TAYLOR NIGEL PHILIP ; HORBURY JOHN (GB); ASTRAZENECA UK LTD (GB)) 19 February 2004 (2004-02-19) page 2, line 18 - page 2, line 30; example 4	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 November 2004

Date of mailing of the international search report

02/12/2004

Name and mailing address of the ISA

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Usue111, A

**INTERNATIONAL SEARCH REPORT**

PCT/GB2004/004133

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: \_\_\_\_\_  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.: \_\_\_\_\_  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.: \_\_\_\_\_  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

on patent family members

PCT/GB2004/004133

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0160804	A	23-08-2001	AU 775569 B2	05-08-2004
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